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COMMENTARY

The control of H5 or H7 mildly pathogenic avian influenza - a role for inactivated vaccine

David A. Halvorson*

Department of Veterinary Pathobiology, College of Veterinary Medicine, University of Minnesota, Saint Paul, Minnesota 55108, USA.

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*To whom correspondence should be addressed. E-mail halvo002@umn.edu

Fax: 612-625-5203

The control of H5 or H7 mildly pathogenic avian influenza - a role for inactivated vaccine

Abstract

Biosecurity is the first line of defence in the prevention and control of mildly pathogenic avian influenza (MPAI). Its use has been highly successful in keeping avian influenza (AI) out of commercial poultry world-wide. However, sometimes AI gets introduced into poultry populations, and when that occurs biosecurity again is the primary means of controlling the disease. There is agreement that routine serological monitoring, disease reporting, isolation or quarantine of affected flocks, application of strict measures to prevent the contamination of and movement of people and equipment, and changing flock schedules are necessities for controlling AI. There is disagreement as to the disposition of MPAI infected flocks: some advocate their destruction and others advocate controlled marketing.

Sometimes biosecurity is not enough to stop the spread of MPAI. In general, influenza virus requires a dense population of susceptible hosts to maintain itself. When there is a large population of susceptible poultry in an area, use of an inactivated AI vaccine can contribute to AI control by reducing the susceptibility of the population.

Does *use of* inactivated vaccine assist, complicate or interfere with AI control and eradication? Yes. It assists MPAI control (which may reduce the risk of highly pathogenic AI [HPAI]), but unless steps are taken to prevent it, vaccination may interfere with sero-epidemiology in case of an HPAI outbreak. Does *lack of* vaccine assist, complicate or interfere with AI control and eradication? Yes. It assists in identification of sero-positive (convalescent) flocks in a HPAI eradication program, but interferes with MPAI control (which in turn may increase the risk of emergence of HPAI).

A number of hypothetical concerns have been raised about the use of inactivated AI vaccines. Infection of vaccinated flocks, serology complications and spreading of virus by vaccine crews, are some of the hypothetical concerns. The discussion of these concerns should take place in a scientific framework and should recognize that control of MPAI reduces the risk of HPAI. That inactivated vaccines have reduced a flock's susceptibility to AI infection, have reduced the quantity of virus shed post challenge, have reduced transmission and have markedly reduced disease losses, are scientific facts.

The current regulations preventing vaccination against H5 or H7 MPAI have had the effect of promoting circulation of MPAI virus in commercial poultry and live poultry markets. In the absence of highly pathogenic avian influenza, there is no justification for forbidding the use of inactivated vaccine.

Introduction

Avian influenza (AI) is a disease of poultry characterized by lethargy and respiratory signs caused by type A influenza virus infections. Influenza viruses are subtyped based on antigenicity of surface projections called haemagglutinin (H) and neuraminidase (N). There are 15 known haemagglutinins and 9 known neuraminidases, all of which have been detected in birds. Subtype designations include the H and N type, for example, H1N1 or H5N2.

Another way avian influenza viruses are characterized is by pathotype. Two pathotypes are recognized. Most AI viruses are mildly pathogenic (MPAI); they produce few, if any, clinical signs when experimentally inoculated into growing chickens or turkeys. In poultry flocks MPAI viruses may be associated with mild or severe clinical signs, egg production loss, mortality and financial loss, depending on the virus, the host, secondary infections and environmental factors. Occasionally an AI virus is highly pathogenic (HPAI). This means that it is usually associated with high morbidity and mortality in commercial flocks, and it causes high mortality when experimentally inoculated into young chickens or turkeys. A diagnosis of HPAI triggers government action to eradicate the disease usually by "stamping out", meaning slaughter and burial or burning of carcasses. Although most H5 and H7 viruses are MPAI, so far all HPAI viruses have been of the H5 or H7 subtypes. The fact that all HPAI viruses have been H5 or H7 has led to confusion among some that all H5 and H7 viruses are HPAI.

There is growing recognition that outbreaks of MPAI are an important source of HPIA viruses (Halvorson, 1997). A chicken outbreak of MPAI in 1983 mutated into HPAI in 1983-1984, resulting in a federal-state eradication program that required the depopulation of 17 million birds (Eckroade & Silverman-Bachin, 1986). Similar outbreaks of MPAI in Mexico in 1994 and Italy in 1999 also mutated into HPAI causing severe losses. (Villarreal & Flores, 1997 and Capua & Marangon, 2000). Laboratory studies of MPAI viruses of chicken and swan origin have yielded HPAI viruses (Swayne, 1997; Ito, 2001).

Epidemiology

Waterfowl and shorebirds (wild and domesticated) are the major natural reservoir of influenza viruses. Wild waterfowl are asymptomatic, may excrete virus in faeces for long periods, may be infected with more than one subtype and often do not develop a detectable antibody response. Influenza virus has been recovered directly from lake and pond water utilized by infected wild ducks. Contact between these birds and range-reared commercial flocks is an important factor in some outbreaks. This source of infection often results in a seasonal incidence in some states.

Another reservoir is the live poultry market. Live poultry markets have existed in large cities forever but they are an emerging phenomenon in some areas. They serve as wholesale and retail focal points for gathering and housing many species of poultry that are then sold. These facilities are usually not depopulated. The continuous supply of susceptible poultry in such markets enhances opportunity for viral replication and mutation, and this in turn enhances the opportunity for viruses to be carried from the markets back to susceptible poultry flocks.

Although waterfowl shed virus in their droppings for long periods, most viral shedding from infected poultry stops after seroconversion. In poultry, influenza virus is released in respiratory secretions and excretions and droppings of infected birds where it is protected by organic material. The virus is labile in warm conditions, but can survive for months in a cold environment. Once AI is introduced into the poultry industry it is transmitted from farm to farm by direct and indirect contact. AI viruses are transmitted by movement of poultry and manure

and on contaminated shoes, clothing, crates, and other equipment. Thus, people and equipment coming in contact with poultry and poultry manure are associated with spread of the disease.

Influenza virus has been isolated from turkey eggs and semen, but there is no evidence of egg transmission. Improper disposal of infected eggs could potentially expose other susceptible birds, but such transmission has not been observed.

Prevention and control

Biosecurity is the first line of defence against all AI viruses (Beard, 1981). Preventing the introduction of AI by eliminating all contact between commercial poultry and wild birds, swine farms and live poultry markets is a common, routine and successful practice. However, occasionally AI gets introduced into a commercial poultry population. When it does, most routine biosecurity is inadequate and a heightened level of biosecurity is necessary to control the spread.

Once MPAI is introduced into the poultry industry, control is largely dependent on voluntary efforts, since there are no official government eradication programs (Poss, 1986).

- Routine serological monitoring of blood or egg yolk antibody is used in areas where AI has been a problem. This effort provides early detection of an outbreak and permits other measures such as isolation and sanitation to be used early.
- Reporting outbreaks to industry personnel who are in direct or indirect contact with poultry is necessary so that people can take appropriate measures
- Voluntary isolation of infected flocks is the responsibility of the owner and is necessary to prevent transmission to other flocks. Virus shedding declines as the flocks seroconvert, so isolation is especially important early in the course of infection. (Often doing nothing is the single most important thing to reduce the spread of disease.). Rigorous measures to prevent the contamination of and to control the movement of people and equipment are required in order to stop this disease. Careful and effective attention to the most likely sources of AI spread will result in a successful disease control program. Too much attention directed at the least likely sources of disease will result in an unsuccessful program!
- Different industries in different areas take different approaches to the next step. Controlled marketing of flocks after they have recovered from infection is common in the turkey industry. In some broiler producing states, voluntary destruction of infected flocks is encouraged.
- Rescheduling flocks is necessary to make sure there is no active AI virus on the farm before another flock is placed.

There is little disagreement that all outbreaks of MPAI should be controlled with some urgency. However, there are no government policies to help with control. Further, there is no indemnity program in most states or countries to fund aggressive killing and destruction of MPAI infected flocks. Occasionally, states or industry groups in the United States have had funds to indemnify the destruction of a few flocks, but these monies are quickly depleted in a large outbreak. In the United States, there are no reports of industry-funded or state-funded destruction of ten or more flocks involved in a MPAI outbreak. We can conclude that destruction of flocks without indemnity or with industry indemnity will not occur in a large outbreak, but may possibly be successful when applied to the index case.

Once an H5 or H7 MPIA outbreak gets started and has infected more than five to 10 flocks of poultry, it is very unlikely that voluntary industry or state-funded destruction will take place. It is at this point that discussions about control strategies are needed. Are conditions favorable for biosecurity alone to control the disease, or is there a dense population of susceptible birds under multiple management in the area?

It has been suggested that a change in policy from ignoring to eradicating H5 and H7 MPAI should be considered (Capua *et al* 2000a). If governments are willing to indemnify producers for flocks destroyed because of MPAI, then prohibition of killed vaccine may be rational. Conversely, if governments are not prepared to pay for industry losses due to MPAI there is no rationale for prohibition of killed vaccine use.

Under conditions of high poultry density or multiple poultry enterprises in one area, the highest level of biosecurity may not be adequate to control the spread of AI. These two factors (high bird density and multiple enterprises) were characteristics of the MPAI outbreaks in Pennsylvania, Mexico and Italy that resulted in mutation to HPAI viruses. Dense populations of susceptible birds under multiple management are the conditions most likely to promote spread of AIV. Under these conditions, biosecurity alone is not likely to be a successful control strategy. A successful strategy requires reducing the susceptibility and the density of the poultry population, since reducing the number of poultry companies is unlikely to be acceptable to the companies involved.

Poultry density in an area is reduced by changes in the placement schedule (Poss, 1986). Placing susceptible poultry into an active AI area is "adding fuel to the fire" and counters the positive impact of biosecurity. AI transmission is not associated with sero-positive flocks (Kradel, 1992). Leaving infected, sero-positive flocks in the building until they are ready to market and leaving poultry buildings empty until the immediate area is free of active infection are ways to reduce the density of the susceptible population. There are limits, however, to this procedure because growers cannot tolerate, for long periods of time, the financial impact of empty buildings.

Vaccination

As controlled marketing and rescheduling reduce the bird density in an area, controlled immunization with an inactivated vaccine can reduce the susceptibility of the population. Vaccination is the second line of defence against AI (Beard, 1981, 1992).

It is well accepted that vaccination of poultry with non-H5 or non-H7 killed influenza vaccine is an effective tool in the prevention and control of MPAI. In the United States, H1N1 is perhaps the most widely used AI vaccine subtype (Halvorson, *et al* 1997). Its use in turkey breeders is reported in states with large swine populations.

It is acknowledged that eradication of H5 or H7 HPAI by stamping out is required by treaty. Using vaccine to aid in the control of HPAI is a political issue not likely to be changed by this discussion. Few people would propose using vaccine to aid in the control of HPAI, although in some countries financial constraints preclude wholesale slaughter and burial; in some countries export markets are not an issue and a slow systematic program of vaccination and controlled marketing might be used as a means to eradicate HPAI; and in some HPAI outbreaks the stamping out attempts may be unsuccessful. Although the rationale for using controlled vaccination might be similar for both HPAI and MPAI, government eradication programs for HPAI accompanied by indemnity payment means the government determines the rules for how

the eradication program is conducted. The question remains, "Should government set the rules when no indemnity is paid?"

The purpose of this paper is not to discuss using inactivated AI vaccines for non-H5 and non-H7 MPAI. Such use is widely, if not universally, accepted. Nor is it to address the use of vaccines for HPAI. HPAI outbreaks precipitate a government response where government makes the rules and pays the bills. The purpose is to discuss the control and ultimate eradication of H5 or H7 MPAI and ask, "Should inactivated vaccine be available as an aid in the control of H5 and H7 MPAI?"

A discussion of the role of vaccination in influenza control must begin with the conclusion that uncontrolled MPAI may allow the emergence of HPAI (Halvorson, 1997; Capua & Marangon, 2000). At the First International Symposium on Avian Influenza, Beard stated (Beard, 1981) that "With the ubiquitous nature of AI viruses in free flying birds, it may be that vaccination…may be the most feasible tool…to soften the sting of AI." Killed vaccines against influenza have been used successfully in a wide variety of species. Because birds are susceptible to all 15 haemagglutinin subtypes, preventive vaccination prior to an outbreak is not practical. Once a subtype is identified in poultry and biosecurity practices appear to be inadequate, however, controlled vaccination is a tool to reduce the susceptibility of poultry populations and to help bring the outbreak under control.

Concerns about the availability and use of inactivated AI vaccines

Considerations that influence decisions on vaccination have been discussed at length (Beard, 1981, 1986, 1992; Halvorson, 1986; Donahoe, 1997; Halvorson, 1997). There is a difference of opinion as to whether vaccination for AI assists, complicates or interferes with eradication (Beard, 1986). On the one hand, regulatory veterinarians say that if killed vaccines are used the MPAI field virus may replicate - clouding the epidemiological picture; The MPAI field virus might mutate to HPAI; therefore restrictions are justified when killed vaccines are used. On the other hand, some industry veterinarians say the government does not want to pay for the cost of controlling MPAI but wants to set rules that restrict industry's ability to control the disease.

Beard has suggested that vaccination as part of an eradication effort could be justified when that plan incorporated controlled marketing of vaccinated and convalescent flocks before a quarantine was released (Beard, 1986). With MPAI outbreaks, although no official eradication effort is usually involved, it is suggested here that vaccination with inactivated AI vaccine is likewise justified when the poultry industry is trying to eradicate the infection and likewise isolates vaccinated and convalescent flocks until they are marketed.

- ***Will vaccination with inactivated vaccine protect against infection or shedding?*** A common objection to the use of inactivated vaccine is said to be that if a vaccinated flock is exposed to field virus, birds may be infected and shed virus. The genesis of this concern was the observation that Newcastle vaccine used in the California velogenic viscerotropic Newcastle disease (VVND) outbreak impaired the detection of VVND infected flocks (Beard, 1986). In spite of this concern, NDV vaccination was used, and continues to be used, in the U.S. People who object to the use of inactivated AI vaccines base their objections on experimental studies showing partial failure of such vaccines to completely block infection and shedding when high doses of challenge virus are used.

  Unrealistic expectations aside, laboratory results have shown that vaccination eliminates or greatly reduces shedding of virus in experimentally challenged birds. Brugh reported that

vaccination of leghorns totally stopped cloacal shedding post-challenge (Brugh & Stone, 1986). It has been shown that vaccination of turkeys reduced the number of infected birds and quantity of virus shed after experimental challenge; so that if a vaccinated flock gets infected it will excrete approximately 99% to 99.99% less virus than a nonvaccinated infected flock (Karunakaran, 1987).

Field results have not shown vaccine to increase the risk of undetected infection; in fact, field experience has indicated that vaccination greatly enhances a control program. The Utah experience in 1995 is an example of the effectiveness of AI vaccine when used early in an MPAI H7 outbreak. In a dense turkey production area, new cases of AI in turkeys stopped six weeks after the initiation of a widespread vaccination of over 200 flocks with a killed H7 vaccine and the disease was subsequently eliminated (Halvorson, *et al*, 1997). The objection to the use of vaccine because some birds may become infected on exposure to field virus must be weighed against what happens in a non-vaccinated flock. In a non-vaccinated flock, exposure to field virus will result in 100 to 10,000 time more virus production. There is no way a vaccinated flock can be a greater threat to disease control than a non-vaccinated flock that breaks with AI.

- ***Will vaccination protect against transmission*?** Related to the previous concern, some have suggested that vaccinated flocks are a risk for transmitting AI to other flocks. Epidemiological observations have shown that serologically positive birds are not associated with AI transmission (Kradel, 1992). Recent experimental studies have demonstrated that AI vaccine prevents or reduces transmission (Swayne, *et al* 1997). Once again, it is important to weigh this concern against what happens to a non-vaccinated flock when exposed to field virus. Unquestionably a non-vaccinated flock exposed to AI is more likely than a vaccinated flock to be a source of transmission to other flocks.

- ***Will vaccine-induced antibody interfere with serology and epidemiology?*** Serology is used as a surveillance tool to detect seropositive (convalescent) flocks. The antibody induced by circulation of MPAI viruses, like the antibody induced by inactivated vaccines, is detected by the agar gel precipitin (AGP) test. Whole virus vaccines elicit antibodies that react with the AGP test and are indistinguishable from antibodies from the field virus. However, it is important to remember that with the AGP test, antibodies to MPAI are indistinguishable from antibodies to HPAI. Combined presence of HPAI and MPAI viruses also complicates the interpretation of diagnostic results (Capua & Marangon, 2000). Clearly it is preferable to deal with vaccine-induced antibody in a MPAI outbreak rather than to deal with MPAI-induced antibody in a HPAI outbreak.

  Monitoring based on the AGP test is used to detect flocks that have been infected. Even though vaccinated and convalescent flocks are not associated with AI transmission, non-vaccinated sentinel flockmates can and should be left in the vaccinated flocks. To assure that seropositive flocks are not infected, these sentinels can be serologically monitored periodically to detect evidence of AI infection until the vaccinated flocks are marketed. Other approaches to avoid the complication of distinguishing vaccinated from non-vaccinated birds are to use a virus with a heterologous N for the vaccine or use a recombinant HA vaccine (Capua *et al* 2000b). In the case of the former, a neuraminidase inhibition test or an N-specific ELISA can be used and in the case of the latter the AGP test will be negative in vaccinated non-infected birds. As suggested by Beard, vaccinated and convalescent flocks can be treated in the same way- isolated until marketed (Beard, 1986)

- ***Will vaccination crews spread disease?*** Transporting people and vaccination equipment from farm to farm is a risk for transmission of AI, but blood sampling crews, bird-moving crews and depopulation crews are also a risk. This risk must be managed.

- ***Will use of vaccine "send the wrong message?"*** The origin of this concern seems to be the statement that "reliance on AI vaccination *instead of* eradication could have an affect on poultry commerce" (emphasis mine; Beard, 1992). Since there are rarely any official eradication programs for MPAI, we can assume this statement refers to HPAI outbreaks. The reason for this concern was stated to be the belief by some that vaccination could result in contaminated meat entering channels of commerce. Because MPAI viruses have never been detected in meat, the issue of vaccine in MPAI outbreaks should not present a problem. Further, we are considering vaccination as *part of* a control program, not *instead of* a control program. As far as vaccinated flocks being a risk, there can be no doubt that a vaccinated flock poses less risk than a non-vaccinated infected flock. The suggestion that vaccine use sends the wrong message must be balanced with the implied message when H5 and H7 MPAI outbreaks are ignored by governments. It is the responsibility of the US and the EU to send the message that they are eliminating MPAI with all the means at their disposal. What message is sent when H5 or H7 MPAI is allowed to circulate in the poultry industry or the live poultry markets?

- ***Will government indemnify producers for losses experienced when flocks get H5 or H7 MPAI?*** With no indemnity from government, vaccine as a safety net is critical (Beard, 1992). The likelihood of indemnification decreases as the poultry farm size increases. Without such a program, certain parts of the industry are more prone to disastrous effects of MPAI than others. Farmers with egg production birds, with very young chicks or poults or with meat birds within two weeks of market are at the greatest economic risk. If governments are not going to indemnify losses, they have no justification prohibiting vaccine use. If there is industry pressure to voluntarily destroy an AI sero-positive flock, a producer may delay reporting or may be motivated to market an actively infected flock.

- ***Will lack of a vaccine give a producer an incentive to expose his flock to infected birds?*** During an AI outbreak, the lack of a vaccine or lack of permission to use an existing vaccine provides the egg producer with an incentive to expose replacement pullets or replacement breeders to AI prior to the onset of egg production (Halvorson, 1997). This is done to reduce the risk of a severe egg production drop should MPAI infect a flock while in egg production. A grower may also similarly be motivated to expose growing birds well before the date of slaughter to reduce potential losses associated with airsacculitis condemnation at the processing plant. While intentional exposure may protect the producer against financial loss, it does not contribute to disease control. Intentional exposure is rumoured to have occurred in Minnesota, Pennsylvania and Mexico (Halvorson, 2000).

- ***Will one control measure fit the needs of the broiler, layer and turkey industries?*** This question implies that vaccination would be used *instead of* rather than *in conjunction* with biosecurity. The needs of the broiler, layer and turkey industries may be different but they all benefit from elimination of a disease threat in an area. If the overall goal of elimination of MPAI is recognized, then each industry can go about it using the most effective and applicable measures available. Long-lived birds (breeders and commercial layers) are most suitable candidates for vaccination, and the protection induced by killed AI vaccine against

egg production losses are clear. Market turkeys, because of their size and value at market, also may benefit from vaccination during an MPAI outbreak. It is frequently stated that vaccination of broilers would not be suitable, although research has shown great benefit to the day-old immunization of broilers with killed oil emulsion AI vaccine (Brugh & Stone, 1986).

- ***Will vaccine use aid in the emergence of virulent variant AI strains?*** In the world-wide human population influenza virus is constantly mutating until it changes sufficiently that it bypasses the existing immunity in humans and starts a new epidemic. This phenomenon has not been seen in poultry because AI outbreaks usually occur in immunologically virgin poultry flocks. If a large population of poultry were immunized (by either natural infection or by vaccination), it is reasonable to assume that a variant could emerge. Hinshaw (Hinshaw, *et al* 1990) showed that this could occur in a laboratory situation. More recent research showed protection from a single recombinant vaccine against diverse H5 challenge viruses from four continents isolated over a 38-year-period (Swayne *et al.*, 2000). What the effect of continuous vaccination in an area would be is not clear. This potential is one reason that reliance on vaccination alone is not a good strategy for MPAI control. However, it is also a reason not to allow MPAI outbreaks to spread unchecked.

Conclusion

In spite of hypothetical concerns, inactivated AI vaccines have contributed successfully to preventing morbidity, mortality and egg production loss, reducing economic loss and controlling the spread of disease. Contrary to the prevailing attitude among some regulatory officials that vaccines are a last resort, there is rationale and evidence to support their immediate use in helping to stop a H5 or H7 MPAI outbreak.

Controlled vaccination against MPAI H5 and H7 should be available as part of a science-based influenza control strategy that includes tight biosecurity and:

- monitoring all flocks at risk,
- using controlled vaccination for flocks deemed to be at risk by industry veterinarians (where regulatory veterinarians are informed of all vaccine use),
- monitoring sentinel birds left in the vaccinated flocks, or other appropriate monitoring methods,
- isolating or quarantining convalescent and vaccinated flocks, and
- controlled marketing of convalescent and vaccinated flocks.

It is time for the regulatory veterinarians to take a leadership role in this issue of vaccination for MPAI. The current regulations preventing vaccination against H5 or H7 MPAI have had the effect of promoting circulation of MPAI virus in commercial poultry and live poultry markets. Uncontrolled H5 and H7 MPAI has already been shown to mutate to HPAI. Current international regulations, as interpreted, prevent veterinarians from adequately fighting mildly pathogenic avian influenza. It is time to work on an international basis to change the interpretation or to correct the regulations.

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